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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
KANAME KAWASUGI	: EXAMINER: WEDDINGTON, K. .
SERIAL NO: 10/572,557	:
FILED: MARCH 17, 2006	: GROUP ART UNIT: 1614
FOR: MEDICINAL COMPOSITION	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This brief is submitted in response to the rejection dated January 30, 2008 and the Advisory Action dated August 25, 2008.

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REAL PARTY OF INTEREST

The real party of interest herein is Dr. Kaname Kawasugi, the named inventor.

RELATED APPEALS AND INTERFERENCES

To the best of Appellants' knowledge, there are no other appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this appeal.

STATUS OF CLAIMS

Claims 10 and 17-21 are active in this application.

Claims 10 and 17-21 are rejected.

Claims 10 and 17-21 are appealed

JURISDICTIONAL STATEMENT

The Board of Patent Appeals and Interferences has jurisdiction pursuant to 35 U.S.C. § 134.

STATUS OF AMENDMENTS

No outstanding amendments are present in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the pending, rejected and appealed independent claim is outlined below with reference to exemplary support in the originally filed application.

The claimed invention as set forth in Claim 17 (Appendix I) is directed to a medicinal composition **{page 5, 1st ¶}** comprising an insulin resistance-improving drug and vitamin B_1 or derivative**{age 4, ¶ 2-4)}** thereof in an amount effective for inhibiting at least one side effect of said insulin resistance-improving drug **{page 4, last ¶, page 5, 2nd ¶ to page 6, 3rd ¶}**, which side effect is selected from the group consisting of edema, heart enlargement and anemia **{page 1, 1st ¶, page 3, 3rd ¶, page 6, last ¶ to page 5, line 5}**, and wherein the insulin resistance-improving drug is selected from the group consisting of pioglitazone, rosiglitazone and CS-011, and salts thereof **{page 4, 2nd ¶}**.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole rejection to be reviewed on appeal is whether Claims 10 and 17-21 are properly rejected under 35 U.S.C. 103(a) over US 4,687,777 (Meguro et al), US 5,002,953 (Hindley), FR 2,832,064 (Gerard et al), US 6,251,926 (Momose et al) and US 6,166,219 (Yamasaki et al) in view of US 5,977,073 (Khaled) or US 6,660,293 (Giordano et al), evidenced by the publication of Tamai (Japanese Journal of Clinical Medicine, Vol. 57, No. 10, pages 200-2003).

ARGUMENT

In rejecting a claim under 35 U.S.C. § 103(a), the Patent Office must support its rejection by "substantial evidence" within the record,[1] and by "clear and particular" evidence[2] of a suggestion, teaching, or motivation to combine the teachings of different references. As discussed below, there is no substantial evidence, nor clear and particular evidence, within the record that teaches all of the limitations of the pending claims. Without such suggestion or teaching and absent improper hindsight reconstruction,[3] the pending claims are believed to be non-obvious and patentable over the applied references.

The inventor discovered that the side effects caused by the administration of an insulin resistance-improving drug to a patient in need thereof can be inhibited when the drug is administered simultaneously with vitamin B_1 or a derivative thereof. The applied prior art discloses nothing more than that the

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[1] In re Gartside, 203 F3d 1305, 53 USPQ2d 1769 (Fed. Cir. 2000) (holding that, consistent with the Administrative Procedure Act at 5 USC 706(e), the CAFC reviews the Board's decisions based on factfindings, such as 35 U.S.C. § 103(a) rejections, using the 'substantial evidence' standard because these decisions are confined to the factual record compiled by the Board.)

[2] In re Dembiczak, 175 F3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, although 'the suggestion more often comes from the teachings of the pertinent references.' The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.") (emphasis added).

[3] See MPEP 2141, stating, as one of the tenets of patent law applying to 35 USC 103, that "[t]he references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention."

presently-recited insulin resistance-improving drugs are known for this utility, and that vitamin B_1 or derivatives thereof have been included in various nutritional compositions for various purposes.

Further, and of significance in the fundamental misunderstanding of the applied art, insulin therapy (and the patients that receive such therapy) is different from insulin sensitizer therapy and as such the cited Khaled and Giordano patents are not particularly relevant. The Tamai publication does not actually show that vitamin B1 is a known treatment for insulin sensitizers but rather that Tamai focuses on B6 for insulin-receiving patients.

Evidence that shows the differences between insulin therapy and insulin sensitizer therapy was submitted in the Declaration under 37 C.F.R. § 1.132 by the named inventor Dr. Kaname Kawasugi (hereinafter "Declaration").

As explained by Dr. Kawasugi in the Declaration:

The insulin resistance-improving drugs pioglitazone, rosiglitazone and CS-011 were known as shown in some of the publications cited by the Patent Office. (Declaration at ¶5) However, what is described in Khaled and Giordano with regards to vitamin B_1 or derivatives thereof is not particular informative as to the inclusion of vitamin B_1 in compositions with insulin resistance-improving drugs. (Declaration at ¶6)

Khaled discusses treatment of an immune disorder with a nutrient composition which may contain thiamine and as one of such disorders, diabetes is mentioned in column 3. Giordano et al a prophylactic and therapeutic

supplementation of nutrition that may contain thiamine, and may be administered to patients with various diseases or disorders, including poorly controlled diabetes (paragraph bridging columns 1 and 2). (Declaration at ¶7)

However, diabetes and insulin therapy (and the patients that receive such therapy) as is the case with Khaled and Giordano is different from insulin sensitizer therapy and as such the Khaled and Giordano patents are not relevant to the question of whether one would have included vitamin B1 with insulin resistance-improving drugs. (Declaration at ¶8)

In the rejection, the newly cited Tamai publication also is not relevant to the question of whether one would have included vitamin B1 with insulin resistance-improving drugs. In fact, it seems there is a fundamental misunderstanding about what is described in the Tamai reference. (Declaration at ¶9)

By way of background, diabetic patients receiving insulin therapy (like those that are targeted in Tamai, Khaled and Giordano) (A) are not the same patients that would receive therapy with insulin-sensitizer drugs and (B) are contraindicated for doing so. (Declaration at ¶10)

An insulin-resistance improving (Insulin sensitizer) drug is used when, although the endogenous insulin is secreted, the clinical condition is such that the muscle sensitivity is deteriorating. In contrast, insulin therapy is used in the clinical condition such as type 1 diabetes and depletion of endogenous insulin. It is called the "Insulin sensitizer" but the concept is different. Insulin therapy

patients generally do not take insulin sensitizer drugs, and patients taking insulin sensitizer drugs generally do not have insulin therapy. (see attached documents, Harrison's Principles of Internal Medicine, 15th Ed, Braunwald *et al.* (Ed.), McGraw-Hill, pp. 2109-2111, 2123, 2129-2135 and the underlined portions therein; *N Engl J Med* 358;3 January 2008 "Management of Type 2 Diabetes; McMahon *et al.*, *N Engl J Med* 356;5 February 2007 "Inhaled Insulin for Diabetes Mellitus"; and the attached printouts from the American Diabetes Association webpage (www.diabetes.org) which outlines the conditions, treatments, and drugs used to combat those disorders). (Declaration at ¶11) Indeed, insulin therapy and insulin-resistance improving or insulin sensitizer drugs are contraindicated (e.g., see the discussion of thiazolidinediones, a class of insulin sensitizers, in the sentence bridging pages 1114-115 in Järvinen *N Engl J Med* 351;11 September 2004). Contraindicated means "to make (a treatment or procedure) inadvisable" (http://www.merriam-webster.com/dictionary/contraindicated). (Declaration at ¶12)

Tamai refers to reduced usage of insulin, i.e., less insulin in an insulin administration protocol, but this discussion does not link to the reduction of side-effects due to insulin-resistance improving drugs. This is not surprising as noted immediately above, the two types of therapy are contraindictive of each other. Thus, at best Tamai only suggests the relationship between vitamin B1 and diabetic peripheral neuropathy (treated with insulin not with the contraindicated insulin sensitizers). (Declaration at ¶13)

Further, Tamai does not actually link vitamin B1 supplementation with insulin therapy but rather vitamin B6 with insulin therapy, much like that which is described in the Harrison's textbook (see pp. 2123, col. 1, paragraph titled "Treatment"). (Declaration at ¶14)

The Patent Office seems to rely on the portions of the Abstract that mentions plasma vitamin B1 and then in a second portion of the English Abstract suggests administering vitamins to diabetic patients.. Reliance on this Abstract is misplaced and when the entirety of Tamai is reviewed, it does not appear that Tamai ever correlates B1 with insulin and the use of B1 in diabetic patients but rather focuses on B6 in that manner. (Declaration at ¶15)

The focal description in the English abstract has a counterpart in the "Conclusion" part of the Japanese description. In the description about vitamin B6, Tamai stated that "in the second half of pregnancy the amount of insulin increases, but B6 deficiency during pregnancy is related to insulin resistance due to pregnancy." There is no other description which implies the reduction of necessary amount of insulin. This indicates that the cited portion of the English abstract is not directed to vitamin B1 but B6. (Declaration at ¶16)

In the "Conclusion" part, Tamai stated that, in recent years, there has been some device not only to improve the secondary-generated vitamin deficiency but also to reduce the amount of insulin required, or to prevent improve the pharmacological action expected to actively administration, and reduce the amount of insulin required, or to prevent complications hoping for the

improvement of pharmacological action. But it is clear that in the underlined sentence, Tamai is referring to B6. (Declaration at ¶17)

Reducing the amount of insulin required for "The insulin therapy (injections)" diabetes patients and decreasing the side effects of insulin sensitizer medicines are problems of completely different dimension. (Declaration at ¶18)

Insulin therapy is a treatment for patients of type 1 diabetes and advanced type 2 diabetes, and for those uncontrollable by oral hypoglycemic agent. It is not for patients who take insulin sensitizer drugs. Again, insulin therapy is a treatment for patients who have a lack of endogenous insulin such as type 1 diabetes, while insulin sensitizer drugs are generally for those whose endogenous insulin secretion is sufficient, but their sensitivity to insulin is decreased. (Declaration at ¶19)

The decreased amount of insulin required in Tamai is the amount of insulin needed in insulin therapy (injections). Also, in Tamai decrease of diabetic complications means common complications of diabetes, including peripheral neuropathy but not side-effects due to insulin sensitizer drugs. (Declaration at ¶20)

Therefore, one would not have derived from this information coupled with what is described in the other documents cited by the Patent Office (e.g., Khaled and Giordano) to combine B1 and insulin sensitizer drugs. (Declaration at ¶21)

Tamai's description regarding the reducing amount of insulin is an object for vitamin B6 but not vitamin B1. Further, reducing the amount of insulin in insulin therapy, and easing the side effects of endogenous insulin are completely different. Thus, the statement by the Patent Office in the rejection on page 3, second paragraph that Vitamin B1 is used with the anti-diabetic agent to reduce insulin requirement as well-known in the art relying on Tamai is a mistake. (Declaration at ¶22)

As Khaled, Giordano and Tamai are all primarily concerned with diabetes (which is treated with insulin) but not patients using insulin sensitizer drugs, I do not agree with the presumption outlined in the last paragraph on page 3 of the Action that combining information related to insulin therapy and insulin sensitizer therapy is something that one would have done, particularly when the recognition in the field is not to do so (i.e., the therapies are contraindicative of each other). (Declaration at ¶23)

Therefore, that the side effects caused by the administration of an insulin resistance-improving drug to a patient can be inhibited when the drug is administered simultaneously with vitamin B_1 or a derivative thereof could not have been reasonably predicted based on what is described in the totality of the publications cited by the Patent Office and the knowledge and experience Dr. Kawasugi have in this field. (Declaration at ¶24)

Persons having ordinary skill in the art normally seek "to improve upon what is already generally known." *In re Peterson*, 315 F.3d 1325, 1330, 65

USPQ2d 1379, 1382-83 (Fed. Cir. 2003). However, before persons having ordinary skill in the art would want to optimize the choice or use of components in a claimed composition, the prior art must at least generally recognize the problems and generally suggest the components the claimed composition utilizes to achieve its goals. To establish that Applicants' claimed composition would have been obvious to a person having ordinary skill in the art, the prior art must reasonably suggest that persons having ordinary skill in the art do what Applicants claims require. Here, the only suggestion to do what Applicants have done is Applicants' own disclosure, i.e. hindsight.

Where, as here, the rejection of the subject matter Applicants claim is based on hindsight, the rejection is improper.

CONCLUSION

Accordingly, in view of the above remarks and reasons explaining the patentable distinctness of the presently appealed claims over the prior art, Appellants request that the Examiner's rejections be REVERSED.

Respectfully submitted,

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APPENDIX 1 (CLAIMS)

Claims 1-9 (Canceled).

Claim 10 (Rejected): The medicinal composition claimed in Claim 17, comprising 5 to 300 mg of insulin resistance-improving drug, and 1 to 500 mg of vitamin B_1 or derivative thereof for one unit dose.

Claims 11-16 (Canceled).

Claim 17 (Rejected): A medicinal composition comprising an insulin resistance-improving drug and vitamin B_1 or derivative thereof in an amount effective for inhibiting at least one side effect of said insulin resistance-improving drug, which side effect is selected from the group consisting of edema, heart enlargement and anemia, and wherein the insulin resistance-improving drug is selected from the group consisting of pioglitazone, rosiglitazone and CS-011, and salts thereof.

Claim 18 (Rejected): The medicinal composition claimed in claim 17, wherein the insulin resistance-improving drug is pioglitazone.

Claim 19 (Rejected): The medicinal composition claimed in claim 17, wherein the insulin resistance-improving drug is rosiglitazone.

Claim 20 (Rejected): The medicinal composition claimed in claim 17, wherein the insulin resistance-improving drug is CS-011.

Claim 21 (Rejected): A method comprising administering the medicinal composition as claimed in claim 17 in an effective amount to a subject in need thereof.

APPENDIX II (EVIDENCE)

1. Declaration under 37 C.F.R. § 1.132 filed in the record on June 30, 2008.
2. (http://www.merriam-webster.com/dictionary/contraindicated, attached to and cited in the Declaration filed in the record on June 30, 2008.
3. Järvinen *N Engl J Med* 351;11 September 2004, attached to and cited in the Declaration filed in the record on June 30, 2008.
4. Harrison's Principles of Internal Medicine, 15th Ed, Braunwald *et al.* (Ed.), McGraw-Hill, pp. 2109-2111, 2123, 2129-2135, attached to and cited in the Declaration filed in the record on June 30, 2008.
5. *N Engl J Med* 358;3 January 2008 "Management of Type 2 Diabetes; McMahon *et al.*, *N Engl J Med* 356;5 February 2007 "Inhaled Insulin for Diabetes Mellitus" , attached to and cited in the Declaration filed in the record on June 30, 2008.
6. Printouts from the American Diabetes Association webpage (www.diabetes.org) , attached to and cited in the Declaration filed in the record on June 30, 2008.

APPENDIX III

RELATED APPEALS AND INTERFERENCES

None.